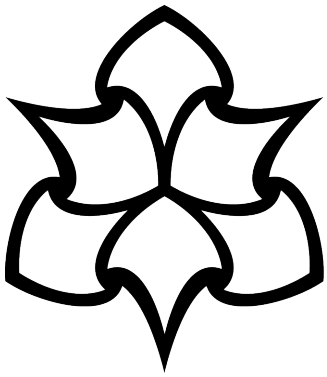

Manchester Metropolitan University

Perazzolo, M, Reeves, ND ORCID logoORCID: https://orcid.org/0000-0001-9213-4580, Bowling, FL, Boulton, AJM, Raffi, M and Marple-Horvat, DE (2020) A new approach to identifying the effect of diabetic peripheral neuropathy on the ability to drive safely. Transportation Research Part F: Traffic Psychology and Behaviour, 69. pp. 324-334. ISSN 1369-8478

Downloaded from: https://e-space.mmu.ac.uk/625363/

Version: Accepted Version

Publisher: Elsevier

DOI: https://doi.org/10.1016/j.trf.2020.01.015

Usage rights: Creative Commons: Attribution-Noncommercial-No Derivative Works 4.0

Please cite the published version

https://e-space.mmu.ac.uk

A new approach to identifying the effect of diabetic peripheral neuropathy on the ability to drive safely

Perazzolo M[1,4], Reeves ND[1], Bowling FL[2], Boulton AJM[2,3], Raffi M[4], Marple-Horvat DE[1]

[1]*Research Centre for Musculoskeletal Science & Sports Medicine, Department of Life Sciences, Faculty of Science & Engineering, Manchester Metropolitan University, Oxford Road, Manchester, UK.*

[2]*Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK*

[3]*Diabetes Research Institute, University of Miami, Miami, FL, USA*

4[1]Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy

Corresponding author

Monica Perazzolo, PhD

Department of Life Sciences

Faculty of Science & Engineering

Manchester Metropolitan University

John Dalton Building, Oxford Road, Manchester M1 5GD UK

Tel: +44 161-247-5429

Email: monica.perazzolo4@gmail.com

Abstract

The purpose of this study was to estimate the potential for impaired driving performance in current drivers with diabetic peripheral neuropathy compared to healthy controls. We analysed, using a driving simulator, three important aspects of driving - use of the accelerator pedal, steering wheel and eye-steering coordination - to test for any differences, and then to integrate these findings to identify a unique pattern of changes in people driving with diabetic peripheral neuropathy. Patients with diabetic peripheral neuropathy displayed differences in use of the accelerator pedal compared to healthy control drivers ($p<0.05$) which could be a direct consequence of their sensorimotor impairment due to diabetic peripheral neuropathy. Drivers with DPN used the more extreme high and low positions of the pedal to a greater extent than the Control group who exhibited a more graded use of the accelerator pedal over the mid-range. Eye-steering coordination was also different in drivers with diabetic peripheral neuropathy ($p<0.05$) and, as it improved during the second drive, becoming closer to healthy drivers' values, the occasional loss of control experienced during driving reduced. These insights demonstrate that diabetic peripheral neuropathy affects multiple aspects of driving performance suggesting the need for an integrated approach to evaluate the potential for driving safely in this population.

1. Introduction

Driving can be considered as a sensorimotor process in which multiple streams of information are combined and processed in order to produce an adequate motor output (Siegler et al., 2001). The speed at which sensory information is processed and the motor reaction times are crucial factors for successfully negotiating difficult or dangerous traffic situations and for avoiding collisions (Anstey et al., 2005).

Different perceptual, cognitive, and motor factors have been associated with driving difficulties and crash incidence (Marmeleira et al., 2009). Primarily, it has been

recognized that age-related changes in sensory, cognitive, and physical abilities, impair driving capability (Kua et al., 2007), and in particular health status (e.g. cardiovascular illnesses, diabetes mellitus, depression, and dementia) can be directly linked to the occurrence of crashes in older drivers (McGwin Jr et al., 2000).

Diabetes leads to a wide range of complications that could impair driving performance (Inkster and Frier, 2013; Seeger and Lehmann, 2011): 1) hypoglycaemia has been recognized as one of the most important risk factors in causing accidents (Cox et al., 2006); 2) diabetic retinopathy leads to visual deficits that can make it impossible to control a vehicle; 3) diabetic peripheral neuropathy (nerve damage and loss of sensation in the feet) may affect the ability to feel the pedals when driving (Inkster and Frier, 2013). The International Diabetes Federation estimated that in 2017 there were 451 million people with diabetes worldwide. These figures were expected to increase to 693 million by 2045 It was estimated that almost half of all people (49.7%) living with diabetes are undiagnosed (Cho et al., 2018). Public Health England estimates that 3.8 million people in England, around 9% of the adult population, now have diabetes (Public Health England press release, September 2016). Up to 50% of these (so 4.5% of all UK adults) will have diabetic neuropathy (Diabetes UK Facts and Stats, October 2016). An estimated 45.5 million people in England hold a full car driving licence (Driver and Vehicle Licencing Agency, 2015). These figures suggest that 2.047.500 individuals, a large number, are driving with diabetic peripheral neuropathy, and if present trends continue, this number will substantially increase. Despite the fact that peripheral neuropathy affects up to 50% of patients, and diabetic peripheral neuropathy (DPN) has been recognized to be one of the most common presentations of diabetes, only a few studies have addressed this complication as a potential factor in impairing driving performance (Meyr and Spiess, 2017; Sansosti et al., 2017; Spiess et al., 2017) so, for these reasons in our research we

tried to offer objective quantitative measures of driving performance impairment while also evaluating the potential for improving (Perazzolo et al., 2019).

Diabetic peripheral neuropathy leads to irreversible diffuse nerve damage (Mendez, 2002; Schaumburg and Spencer, 1979); the progressive loss of both sensory and motor fibres causes a subsequent decrease in neural sensitivity, proprioception and muscle strength (Andreassen et al., 2009; Chiles et al., 2014; Sénéchal et al., 2015; Shun et al., 2004; Simoneau et al., 1995; Vaz et al., 2013). To assess fitness to drive with DPN, considering the wide spectrum of clinical manifestations for this condition, an integrated approach is required covering the different aspects of driving and assessing both sensory and motor system variables. The first important aspect is the control of the pedals. The cutaneous and proprioceptive sensory loss together with the motor dysfunction seen in DPN start from the feet and progressively affect more proximal parts of the lower limbs (King, 2001; Said, 2007); it has already been shown that DPN patients present altered (longer) brake response times compared to diabetic patients without neuropathy and healthy controls (American Diabetes Association, 2013) Another fundamental aspect of driving is eye-steering coordination (Chattington et al., 2007; Land and Lee, 1994). The degree of coordination between eye and steering wheel movements, and their relative timing, substantially determines driving performance (Marple-Horvat et al., 2005), and impaired coordination, for example during alcohol intoxication, is associated with crash incidents (Marple-Horvat et al., 2008). Appropriate eye-steering coordination reflects the way in which the central nervous system has solved the problem of steering, using and combining all available information, including that arriving from the peripheral nervous system (sensory information), but there have been no studies of the effect of diabetic peripheral neuropathy on eye-steering coordination to date.

Until now, literature on driving with diabetes has mainly focused on the risk of\ hypoglycaemic events during driving and the associated incidence of crashes. This current research is an extension of a study in which we demonstrated that motor function impairment due to diabetic peripheral neuropathy can affect driving performance. People with diabetic peripheral neuropathy reduce their overall driving speed for example (Perazzolo et al., 2019). In this report, we present analyses of several fundamental aspects of driving - use of the accelerator pedal, steering, and eye-steering coordination – that can be used in an integrated way to identify any uniquely different pattern of driving in people driving with DPN. The innovative approach of this study consists of assessing whether there are differences in both central (eye-steering coordination) and peripheral (pedal control) components that could potentially have a negative impact on driving performance. Once the risk associated with hypoglycaemic events has been excluded, are there other potential factors that we should consider in order to assess driving fitness in this population?

2. MATERIALS AND METHODS

2.1 Participants

Twenty-two UK active drivers were recruited into two groups: 11 participants with diabetic peripheral neuropathy, DPN (DPN group mean ± SD, age 67 ± 5.0 years, BMI 32 ± 4.2 kg/m^2, n= 9 males; 2 females), and 11 healthy age-matched controls without diabetes (Control group aged 60 ± 11 years, BMI 27 ± 4.4 kg/m^2; 9 males, 2 females). In terms of ethnicity all participants were white British. All participants gave their written informed consent to participate in the study, which received ethical approval from all relevant bodies. The inclusion criteria were: diagnosis of diabetes and diabetic peripheral neuropathy for the DPN group, or absence of diabetes and diabetic peripheral neuropathy in the Control group (confirmed via random blood glucose test <7.8 mmol/l); holding a

current full UK driving licence; driving a car at least once per week. The exclusion criteria were: 1) active foot ulcers on either foot, 2) lower limb amputation involving more than two toes on the right foot, 3) dementia, 4) visual acuity worse than 20/50, 5) proliferative diabetic retinopathy.

2.2 Procedure

Before starting to record we obtained a medical history. We used the modified Neuropathy Disability Score (mNDS), a composite test of multiple sensory modalities, together with the detection of the vibration perception threshold (VPT), using a neurothesiometer (Bailey Instruments Ltd. Manchester, U.K.), to assess the presence and the severity of diabetic peripheral neuropathy (Boulton et al., 2004). Patients were defined as having moderate-severe diabetic peripheral and accepted into the DPN group if they demonstrated a mNDS score of ≥25 and/or a VPT of ≥25 Volts, on either foot. A random blood glucose test was used to confirm the absence of diabetes in controls and to avoid any hypo- or hyperglycaemic influence during the driving task in the DPN group. Blood glucose levels needed to be within a range of 4.5 to 20 mmol/l to progress to the simulated driving task.

Visual acuity was assessed using a Snellen Chart (23 X 35.5 cm) with traditional optotypes. Visual acuity range from 20/200 to 20/20 was tested at 3 meters distance (McGraw et al., 1995). Corrected visual acuity had to be ≥ 20/50 since this is defined by the World Health Organization as “moderate visual impairment”.

2.3 The driving simulator session

The driving simulator consisted of a 42-inch plasma screen, a force feedback steering wheel, accelerator and brake pedal system and car seat. Analogue signals of accelerator

pedal position, horizontal eye movement (calibrated to 1° accuracy), and steering wheel rotation were digitized at 200 Hz using a CED 1401A/D converter (Cambridge Electronic Design, Cambridge, UK). Eye movements were recorded using a remote infra-red eye tracking system (ASL 504, Applied Science Laboratories, Bedford, MA, USA) mounted at dash panel height.

Participants were invited to find a comfortable driving position with adjustment of the simulator construct as needed for individual preference. Specific instructions were given to participants: "drive safely, as you would in a real car on the road". Verbal instruction concerning the car controls was given, including that the car was an 'automatic' so there were only accelerator and brake pedals. The route consisted of a driving environment simplified by the absence of other vehicles and pedestrians, taken from the Colin McRae Rally 2 simulation (Codemaster, Leamington Spa, Warwickshire, UK). The duration of the driving session varied depending on the participant's own chosen speed to travel along a winding country road 3.1 miles long, which included gentle and sharp bends with few straight sections. At the end of the driving session we asked some questions about the experience and about participants' driving habits in real life.

3. DATA ANALYSIS

3.1 The driving simulator session

The task consisted of driving the same 3.1-mile route twice with a rest in between. We analysed data from both drives.

3.2 Accelerator pedal

An analogue sensor in the pedal assembly monitored pedal position (in Volts). This analogue pedal signal was digitized at 200 Hz using a CED 1401 (Cambridge Electronic Design, Cambridge, England) and analysed with Spike 2 Version 5.11 software. The

pedal was calibrated to convert from Volts to degrees; the range of pedal position was from 0° (upper limit) to -20° (fully depressed). We performed a frequency distribution analysis of the digitised pedal signal using Spike 2 software to produce a frequency distribution plot with 0.5 degrees bin width for each individual drive. These individual distributions were then exported into excel to produce a group plot (averaged across all drivers in the group). Difference plots were produced by subtracting one group frequency distribution from another and analysed using SPSS. This frequency distribution analysis reveals how much time in a given journey (expressed as a percentage of the journey duration) drivers spend with the accelerator within a specific 0.5 degrees range (e.g. between 4.5 and 5 degrees depressed). The pattern of pedal usage can then be compared in the same subject under different conditions, or between different subjects. This standard signal analysis approach has been used to establish the pedal usage pattern in a number of different conditions and in different populations.

3.3 Eye-steering coordination

Driving is an everyday example of visually guided behaviour in which the eyes move in coordination with another action (steering) (Chattington et al., 2007). For this reason, we recorded and analysed values that quantify the driver's eye-steering coordination over the drive time: the correlation coefficient and the time lead. The correlation coefficient (r) defines the degree of coordination, and the time lead (Δt) defines the interval by which eye movements lead steering wheel movements across the drive period. Cross-correlograms of horizontal eye vs steering wheel movements were generated using a Spike 2 script. We computed cross-correlograms representing the overall relationship

between drivers' horizontal (left–right) eye movements and their turning of the wheel to negotiate bends in the road for each drive. The horizontal component of eye movements (left-right movements) is fundamental for assessing the anticipatory strategy in which eye movements lead steering wheel movements. Left-right eye movements correlate with steering movements when driving because the driver looks across to the inside of the curve of an approaching bend some time before subsequently turning the steering wheel in the same direction. This study used the same analytical techniques as we have previously used in a realistic simulated driving task, and during natural driving on the road (Chattington et al., 2007; Marple-Horvat et al., 2005; Wilson et al., 2007).

3.4 Steering wheel signal

3.4.1 Familiarization

Driving is a complex task that involves a variety of skills and becomes relatively more automatic with experience because it relies on learned and practised, or routine skills (Freund et al., 2008). For these reasons, we decided to consider separately the initial 3 minutes of the steering wheel signal (degrees) of each drive and observed how the wheel movements appeared in this first phase of practice that we called "familiarization". We chose 3 minutes of driving because drivers reported this to be a time frame long enough to get used to the simulated driving task. Frequency distribution plots of the first 3 minutes of the steering wheel signal were generated for both the Control and DPN group, and then difference plots between the two groups were produced as previously described.

3.4.2 Loss of control events

Visual inspection of the steering wheel signal for a complete drive revealed occasional "loss of control events" that stood out from the rest of the drive as portions where the steering wheel signal had specific different characteristics in terms of amplitude and

frequency. Loss of control events consisted of extreme and inappropriate use of the steering wheel, i.e. large and rapid movements that reached the full range of motion of the steering wheel and/or maintained a repetitive frequency (large swings back and forth) for a period of time. Detection of loss of control events from steering wheel movements took place within the context of looking at all signals (wheel, pedal and eye movements) to understand what was going on. We also looked at a section of driving before and after the loss of control event to identify and analyse the characteristics (frequency and amplitude) of steering wheel movement during a time frame that we considered "normal driving". The two criteria that had to be fulfilled to be a loss of control event were: 1) steering wheel oscillations with a minimum peak to peak value of 150 degrees; 2) at least 3 cycles of oscillations. We used these criteria in the steering wheel signal to identify loss of control events. Our observation was that such large swings of the steering wheel were always accompanied by excursion out of lane (either off the road or onto the wrong side of the road) which the driver attempted but failed to prevent. In real driving on the road, this would represent loss of control of the vehicle, rather than adequate control of the vehicle. For each driver experiencing a loss of control, we produced a steering wheel frequency distribution plot of each loss of control event. We also produced a plot for the whole drive to represent their "baseline condition", so that we could compare these two states in that individual. We were then able to statistically identify (see below) any use of the steering wheel (time spent with the wheel at different degrees of rotation) that differed significantly during a loss of control event compared to baseline driving.

4. STATISTICAL ANALYSIS

We used the Kolmogorov-Smirnov two samples test when we compared accelerator pedal usage over the whole drive, and the steering wheel frequency distribution plots of the first three minutes of driving.

A mixed design factorial ANOVA was used to assess differences between groups (Control, DPN) and drives (Drive 1, Drive 2) concerning eye-steering coordination. Both correlation coefficient (r) values and time lead (Δt) were analysed as dependent variables.

Another mixed design factorial ANOVA was performed in each group (DPN, Control) to assess differences between the steering wheel patterns observed during a loss of control event and its baseline condition during the drives (Drive 1, Drive 2). Differences in age, BMI, neuropathy assessment tests (VTP, mNDS), years of driving licence possession and duration of the drives between groups (DPN vs Control) were assessed using an independent samples Student's t-test.

All statistical tests were analysed using SPSS statistical package (version 22, Chicago, IL, USA) with significance level set at $p<0.05$.

5. RESULTS

The DPN group presented significantly higher values for both the modified Neuropathy Disability Score (mNDS) and the Vibration Perception Threshold (VPT) compared to the Control group ($p<0.05$). Considering that mNDS ranges from 0 to 10, with 0 being detection of every sensation applied to the feet and 10 meaning a complete lack of sensory perception in the feet and therefore severe neuropathy, mNDS scores were: (mean±SD) 8.3 ± 2.0 in the DPN group and 0.5 ± 1.1 in the Control group. Conversely, VPT ranges from 0 to 50 Volts (50 indicating a complete lack of sensory perception in the feet and therefore severe neuropathy) and we found a VPT value of 44 ± 10 Volts in the DPN group and a VPT of 7 ± 3 Volts in the Control group. These values demonstrated that people in the DPN group had severe peripheral neuropathy and confirmed the absence of neuropathy in the Control group. We found a significant difference in the BMI value

between groups ($p<0.05$). There were no significant differences for age and years of driving licence possession between groups ($p>0.05$).

5.1 The driving simulator session

The duration of the first drive was (mean±SD) 12.24 ±3.41 minutes in the DPN group and 8.91±2.45 minutes in the Control group. In the second drive, duration was (mean±SD) 10.60 ±3.3 minutes for the DPN group and 7.96 ±1.4 for the Control group. The DPN group drove significantly slower compared to the Control group in both drives ($p<0.05$).

5.2 Use of accelerator pedal

We found a different pattern in the use of the accelerator pedal between DPN and Control groups ($p<0.05$). In both the first and second drives, drivers with DPN used the mid-range of the pedal less than healthy controls. This is evident in the frequency distribution plots for the two groups and highlighted in the difference plots (Fig.1). The difference plots have 3 clear regions shown in different colours: a mid-range (-1° to -8°) deficit in use of the pedal by drivers with DPN; a peak or surplus in use of the highest positions (0° to -1°); and a second surplus in the low/more extreme positions of the pedal (beyond -8°). The first region (0° to -1°, shown in white) and the third region (beyond -8°, with a black fill) represent the extreme high and low parts of the range of possible pedal positions. The middle region of the frequency distribution, between 1 and 8 degrees (shown in grey), is the mid-range of pedal positions. In the two difference plots on the right-hand side of the figure, bars above the x axis (positive values) show that the DPN group spend more time using the extreme regions/positions (close to zero degrees or beyond 8°) than drivers in the Control group. Bars below the x axis (negative numbers) in the middle of the plots show that the DPN group spend less time using the middle range of the pedal than did the Control group. For clarity, we have superimposed on the frequency distributions the

298 percentage of time that the accelerator pedal was in each of these three regions. In the
299 first drive, significant differences emerged at specific pedal positions in all three regions,
300 high- mid- and low/more extreme (Fig. 1A). Drivers with diabetic peripheral neuropathy
301 used the mid-range of the pedal only 17% of the time, whereas healthy controls used the
302 mid-range of pedal position 50% of the time. A similar deficit in mid-range use of the
303 pedal was seen by drivers with diabetic peripheral neuropathy in drive two (Fig. 1B).
304 Conversely, drivers with neuropathy used the high and low more extreme ranges of pedal
305 position more than healthy controls in both drives.

306

307 Figure 1

308

309

310

311 **5.3 Eye-steering coordination**

312 We obtained good quality eye movement data for all participants in the Control group in
313 both drives. In the DPN group, for technical reasons, (poor quality eye movement signals
314 due to the small size of the pupil or large head movements when driving) we were able
315 to analyse 8 drivers for the first drive, reducing to 5 drivers for the second. We
316 acknowledge the small sample size for this specific variable. The problem was that in this
317 DPN group, whenever drivers were struggling to retain or regain control, they frequently
318 made exaggerated head movements which sometimes resulted in loss of eye tracking. For
319 the second drive, the small sample meant, the statistical power of eye-steering
320 coordination was 0.766, which is below the preferred minimum of 0.8

321 As regards degree of eye-steering coordination, we found a main effect for “group”,
322 drivers in the DPN group had significantly lower eye-steering coordination than Controls
323 ($p<0.05$). We also observed a main effect for “drives” ($p<0.05$) but no significant

interaction effect "group x drives" ($p>0.05$). The correlation coefficient increased significantly between the first and the second drive in the Control group, but a similar increase in the DPN group failed to reach significance ($p>0.05$) (Fig. 2A).

Analysis of time lead values did not show any main effect or interaction effect. In both drives, there were no significant differences in the time lead values between groups ($p>0.05$) or any significant improvement between drives 1 and 2 ($p>0.05$). In the first drive, we observed a longer time lead in the Control group (mean ± SD: Δt -0.71 ± 0.32) compared to the DPN group (Δt -0.44 ± 0.70). During the second drive the DPN group increased their time lead (Δt -0.85 ± 0.59) while the Control group stayed the same (Δt -0.73 ± 0.56) (Fig. 2B).

Figure 2

5.4 Steering wheel signal

5.4.1 Familiarization

In the first three minutes of the first drive, the DPN group steering wheel frequency distribution plots differed from the steering pattern of the Control group at -65°, -55° and -30° ($p<0.05$) (Fig. 3A). These particular differences reflect the general difference that drivers in the DPN group drove for more of the time with the steering wheel turned by larger amounts, and for less time with the wheel turned by smaller amounts. In the second drive, there were no significant differences between the two groups of drivers ($p>0.05$) (Fig. 3B).

Figure 3

5.4.2 Loss of control events

During the first drive, we observed a total of 25 loss of control events: 5 in the Control group and 20 in the DPN group. During the second drive the Control group exhibited no loss of control event, while there were 10 events in the DPN group. Only 27% of the healthy Control group experienced at least one loss of control event during the first drive, compared to 73% of the DPN group.

Group	Total	Drive 1	Drive 2	First 3 minutes	Sharp bend	Other	% participants
Control	5	5	0	2	1	2	27%
DPN	30	20	10	10	9	11	73%

Table 1: Number of loss of control events: total; in a specific drive (Drive1 or Drive2); or in a particular part of the route (first 3 minutes, sharp bend or other).

When considering where these loss of control events happened along the route, we saw that the likelihood these events occurred during the familiarization period (first 3 minutes) or in other unspecified portions of the road was the same in the control group, 40%. As regards the DPN group, the likelihood that a loss of control event occurred during the first 3 minutes was 33% and slightly higher 37% when we considered other road sections. Considering a particularly challenging situation of a sharp (hairpin) bend, the percentage of loss of control events were 20% for Controls and 30% for drivers in the DPN group (Table 1). For drivers in the DPN group, we found a main effect for “drive state” (loss of control, baseline) in both drives ($p<0.05$). In the first drive their pattern of steering (% of time spent with the steering wheel turned by different amounts) during loss of control events differed significantly from the baseline condition (Fig. 4A). The same was true of

the second drive but the two patterns of steering were significantly different over a smaller range of steering wheel positions.

For drivers in the Control group, we could only look for significant differences during loss of control in the first drive, as none occurred during the second drive. During the first drive, we again found significant differences in steering between loss of control and baseline conditions ($p<0.05$) (Fig. 4B).

Figure 4

6. DISCUSSION

We show here, for the first time, differences in driving characteristics in people with diabetic peripheral neuropathy compared to controls without diabetes in terms of accelerator pedal use, steering, and eye-steering coordination; and in loss of control events that indicate impaired driving performance with implications for safety. From a positive perspective, we also show a rapid learning/familiarisation effect in people with diabetic peripheral neuropathy, demonstrating the potential for interventions to improve these driving characteristics.

The first main finding of this study is that drivers with DPN exhibit a significantly different pattern of control of the accelerator pedal than healthy age-matched controls. Drivers with DPN tended to use the middle range of the pedal less, while the Control group exhibited a more graded use of the accelerator pedal over the mid-range of its travel, and less use of the pedal near the extremes of its range. Drivers with DPN switch between extreme high and low positions of the pedal, an approach that seems to suggest

393 and confirm the physiological evidence for reduced fine motor control and proprioceptive
394 function of the lower limb in this population (Forbes and Cooper, 2013).

395 Our second main finding concerns eye-steering coordination. We found a significantly
396 lower correlation between eye and steering wheel movements in people with DPN
397 compared to the Control group. There are reports in the literature that people with diabetes
398 may have nystagmus and reduced slower smooth pursuit eye movements (Darlington et
399 al., 2000). These clinical manifestations associated with diabetes could have a role in
400 disrupting oculomotor coordination and consequently the specific eye-steering
401 coordination normally seen and required during driving. Another explanation for the low
402 eye-steering coordination could be the loss of control events experienced by drivers with
403 diabetic neuropathy. During these events, exaggerated steering wheel movements
404 produced large swings in heading to left and right, and so large swings in the view ahead
405 seen by the driver. Such large swings in the visual world are an effective optokinetic
406 stimulus, which reflexly produce compensatory eye movements. Thus, during a large,
407 rapid steering wheel movement to the left, the visual world swings to the right, producing
408 an optokinetic nystagmus with rightwards slow phase – opposite to the direction of
409 steering wheel movement. This is the inverse of the usual eye-steering coordination when
410 eye movements lead and are in the same direction as steering. Therefore, across the whole
411 drive, there are two distinct and opposite modes of coordination at different times, which
412 when put together would reduce the overall coordination usually seen when fully in
413 control of the vehicle.

414 Driving requires perception and control of self-motion at great speed (Kemeny and
415 Panerai, 2003). In particular, it is necessary to look where you need to steer next (the next
416 bend) early enough in time, and with sufficient distance, to have enough time to prepare
417 steering. For drivers who might be challenged by this, one potential strategy to allow

418 adequate time between looking ahead at the upcoming bend, and subsequently turning
419 the steering wheel, is to reduce driving speed to have a longer interval of time between
420 the eye and steering wheel movements. The slower overall driving speed of drivers with
421 diabetic peripheral neuropathy might therefore be a compensatory mechanism to help
422 mitigate any consequences of the difficulty they experience in the control of the vehicle
423 (Perazzolo et al., 2019). Such an interpretation is supported by the observation that
424 healthy drivers (Controls) showed a time-lead of eye movements over steering of around
425 0.70 seconds in both drives. Similar values have previously been obtained in the identical
426 driving simulation in a younger cohort of healthy drivers who had received the same
427 instruction as in the current study to drive safely as if in a real car on the road (Marple-
428 Horvat et al., 2008). In actual driving on the road, the time lead is even longer, 0.90
429 seconds (Chattington et al., 2007). These observations identify that safe driving in this
430 simulation involves an overall time lead of eye movements over steering of around 0.70
431 seconds, not less.

432 These time leads contrast markedly with the value of 0.44 seconds seen for drivers with
433 DPN in the first drive. It is perhaps not surprising, therefore, that in their first drive,
434 drivers with DPN, exhibiting an unusually low time lead in eye movements relative to
435 steering, experienced loss of control events. It should also be noted, that this short time
436 lead was observed despite people with DPN driving more slowly than controls. It is
437 noteworthy and encouraging that during the second drive, presumably in response to the
438 difficulties experienced in the first drive, drivers with DPN almost doubled their time lead
439 value, and in fact exceeded that seen for the Control group. This might suggest a rapid
440 learning effect after the first drive in people with DPN.

441 When combined with the observation that loss of control events greatly reduced in the
442 second drive, it seems clear that a certain minimum time lead is required to safely

443 complete the driving task. The DPN group's time lead was inversely related to the number
444 of loss of control events: in the first drive a shorter (too short) time lead value of 0.44
445 seconds was accompanied by a higher number of loss of control events. In the second
446 drive DPN's improvement in the time lead value, roughly doubling it to 0.85 seconds,
447 allowed them to greatly reduce, in fact halve, the number of these events. Therefore, as
448 eye-steering coordination changed to more resemble the values seen in healthy
449 individuals, loss of control reduced. For these reasons, we consider time lead values a
450 powerful instrument to assess driving fitness.

451 During the first 3 minutes of the first drive, while familiarizing with the driving simulator,
452 use of the steering wheel showed important, even critical differences, between the two
453 groups of drivers. During this relatively short time frame of driving, we observed a total
454 of 10 loss of control events in the DPN group but just 2 in the Control group, results that
455 suggest that the DPN patients start off worse or take more time to get used to the new
456 'vehicle'. Conversely, use of the steering wheel in the first 3 minutes of the second drive
457 did not show any difference between the two groups, demonstrating that DPN patients
458 can and did improve with practice. Since 30% of the loss of control events occurred at
459 the most difficult corner on the route, and there were roughly 50 bends along the whole
460 route, clearly there was a greater tendency to lose control in the challenging situation, but
461 there was no hard and fast rule that loss of control would happen just at this location.

462 Three quarters of the participants with DPN (73%) but only a quarter (27%) of Controls
463 experienced this 'uncontrolled' pattern of steering wheel movement. We have identified
464 its characteristics – large rapid turns of the wheel back and forth for a number of
465 oscillations. This characteristic pattern is completely different from steering wheel
466 movements seen at other times, during controlled driving which is a quite different
467 'baseline' condition. The differences we have identified provide for discrimination

between normal, safe driving and a different state that represents an increased risk for driving safety.

Limitations

We acknowledge that the present sample size is relatively small, and these results are best considered as preliminary evidence of the several consequences of DPN on driving. Some differences between the groups directly relevant to their clinical conditions do represent residual confounding variables that we have not been able to control for; any effect of these other variables on their driving remains unknown and could be the focus of further studies. Considering the scope and limitations of the test methods used, which are in some ways non-standard (driving) methodology (for instance, we do not present analysis of glances to different areas of the scene), the findings of this study may perhaps be regarded as an initial standard characterization of a new approach to testing driving fitness. This is a characterisation based on standard signals analysis, of the drivers gaze and signals from the car's controls which reflect how the driver is attempting to solve the control problem of driving successfully and safely. These signal processing techniques are capable of identifying impaired driving in quite small groups of individuals. What is more, the group size in the current study (n=11) is comparable with a previous study in the identical simulator and with the same analytical techniques which successfully identified significantly impaired driving due to, in that case, alcohol intoxication; and a study of driving on the road using the same techniques (n=10). Additional signals could also be included in future, in particular to monitor use of the brake (and clutch pedal in a simulated manual gearchange vehicle) and ideally in a variety of driving conditions as would be encountered in a real car on the road. We can say at this stage that the current findings contribute to the emerging global picture of the consequences of DPN on driving

and form the basis for future studies with a wider scope that will further deepen our understanding.

7. CONCLUSION

We have identified, in several fundamental aspects of driving; use of the pedals, the steering wheel, and eye-steering coordination, differences in the driving of individuals who have peripheral neuropathy as a complication of diabetes, compared to healthy age-matched controls. Together, these differences amount to a unique pattern that characterises driving with DPN. These findings shed light on possible driving impairment due to DPN and offer a general method for evaluating it. This set of measurements might be useful for assessing fitness to drive, and an integrated method, including all of these factors, seems the best way of identifying and quantifying changes in driving as a consequence of diabetic peripheral neuropathy, with the possibility to then implement a person-specific behavioural intervention to help drivers to drive more safely for longer. A final goal would be to use these insights to create an algorithm implemented in an automated driver assistance system that could intervene in subtle ways and at crucial times to reduce the risk of serious accidents and help support drivers in real life situations.

Acknowledgments

The authors are grateful to the staff and patients of the Manchester Diabetes Centre at the Manchester Royal Infirmary and Research for the Future, “Help BEAT Diabetes”. This work was supported by funding through the Erasmus Plus programme. Authors declare no conflict of interest.

Keywords: Diabetic peripheral neuropathy, driving simulator, accelerator pedal, eye-steering coordination.

References

American Diabetes Association, 2013. Diabetes and Driving. Diabetes Care 36:S80-S85.

Andreassen, C.S., Jakobsen, J., Ringgaard, S., Ejskjaer, N., Andersen, H., 2009. Accelerated atrophy of lower leg and foot muscles—a follow-up study of long-term diabetic polyneuropathy using magnetic resonance imaging (MRI). Diabetologia 52:1182-91.

Anstey, K.J., Wood, J., Lord, S., Walker, J.G., 2005. Cognitive, sensory and physical factors enabling driving safety in older adults. Clinical Psychology Review 25:45-65.

Boulton, A.J., Malik, R.A., Arezzo, J.C., Sosenko, J.M., 2004. Diabetic somatic neuropathies. Diabetes Care 27:1458-86.

Chattington, M., Wilson, M., Ashford, D., Marple-Horvat, D., 2007. Eye–steering coordination in natural driving. Experimental brain research 180:1-14.

Chiles, N.S., Phillips, C.L., Volpato, S., Bandinelli, S., Ferrucci, L., Guralnik, J.M., Patel, K.V., 2014. Diabetes, peripheral neuropathy, and lower-extremity function. Journal of diabetes and its complications 28:91-95.

Cho, N., Shaw, J., Karuranga, S., Huang, Y., da Rocha Fernandes, J., Ohlrogge, A., Malanda, B., 2018. IDF

Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes research and clinical practice 138:271-81.

Cox, D.J., Kovatchev, B., Vandecar, K., Gonder-Frederick, L., Ritterband, L., Clarke, W., 2006. Hypoglycemia preceding fatal car collisions. Diabetes Care 29:467-68.

Darlington, C.L., Erasmus, J., Nicholson, M., King, J., Smith, P.F., 2000. Comparison of visual–vestibular interaction in insulin‐dependent and non‐insulin‐dependent diabetes mellitus. Neuroreport 11:487-90.

Diabetes UK Facts and Stats, October 2016. https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/DiabetesUK_Facts_Stats_Oct16.pdf

Driver and Vehicle Licencing Agency, 2015. FOI response on driving licence statistics. https://www.gov.uk/government/publications/how-many-people-hold-driving-licences-in-the-uk

Forbes, J.M., Cooper, M.E., 2013. Mechanisms of diabetic complications. Physiological reviews 93:137-88.

Freund, B., Colgrove, L.A., Petrakos, D., McLeod, R., 2008. In my car the brake is on the right: Pedal errors among older drivers. Accident Analysis & Prevention 40:403-09.

Inkster, B., Frier, B.M., 2013. Diabetes and driving. Diabetes, Obesity and Metabolism 15:775-83.

Kemeny, A., Panerai, F., 2003. Evaluating perception in driving simulation experiments. Trends in cognitive sciences 7:31-37.

King, R., 2001. The role of glycation in the pathogenesis of diabetic polyneuropathy. Molecular Pathology 54:400.

566 Kua, A., Korner-Bitensky, N., Desrosiers, J., Man-Son-Hing, M., Marshall, S., 2007. Older driver retraining: A
567 systematic review of evidence of effectiveness. Journal of Safety Research 38:81-90.
568 Land, M.F., Lee, D.N., 1994. Where we look when we steer. Nature 369:742-44.
569
570 Marmeleira, J., Godinho, M., Vogelaere, P., 2009. The potential role of physical activity on driving
571 performance and safety among older adults. European Review of Aging and Physical Activity 6:29-38.
572
573 Marple-Horvat, D., Chattington, M., Anglesea, M., Ashford, D., Wilson, M., Keil, D., 2005. Prevention of
574 coordinated eye movements and steering impairs driving performance. Experimental brain research
575 163:411-20.
576
577 Marple-Horvat, D.E., Cooper, H.L., Gilbey, S.L., Watson, J.C., Mehta, N., Kaur-Mann, D., Wilson, M., Keil, D.,
578 2008. Alcohol badly affects eye movements linked to steering, providing for automatic in-car detection of
579 drink driving. Neuropsychopharmacology 33:849-58.
580
581 McGraw, P., Winn, B., Whitaker, D., 1995. Reliability of the Snellen chart. BMJ: British Medical Journal
582 310:1481.
583
584 McGwin Jr, G., Sims, R.V., Pulley, L., Roseman, J.M., 2000. Relations among chronic medical conditions,
585 medications, and automobile crashes in the elderly: a population-based case-control study. American
586 journal of epidemiology 152:424-31.
587
588 Mendez, J., 2002. Advanced glycosylation end products and chronic complications of diabetes mellitus.
589 Gaceta medica de Mexico 139:49-55.
590
591 Meyr, A.J., Spiess, K.E., 2017. Diabetic driving studies—part 1: brake response time in diabetic drivers with
592 lower extremity neuropathy. The Journal of Foot and Ankle Surgery 56:568-72.
593
594 Perazzolo, M., Reeves, N., Bowling, F., Boulton, A., Raffi, M., Marple‐Horvat, D., 2019. Altered accelerator
595 pedal control in a driving simulator in people with diabetic peripheral neuropathy. Diabetic medicine.
596 https://doi.org/10.1111/dme.13957
597
598 Public Health England press release, September 2016. https://www.gov.uk/government/news/38-million-
599 people-in-england-now-have-diabetes
600
601 Said, G., 2007. Diabetic neuropathy--a review. Nature Reviews. Neurology 3:331.
602
603 Sansosti, L.E., Spiess, K.E., Meyr, A.J., 2017. Diabetic driving studies—part 3: a comparison of mean brake
604 response time between neuropathic diabetic drivers with and without foot pathology. The Journal of Foot
605 and Ankle Surgery 56:577-80.
606
607 Schaumburg, H.H., Spencer, P.S., 1979. Clinical and experimental studies of distal axonopathy—a frequent
608 form of brain and nerve damage produced by environmental chemical hazards. Annals of the New York
609 Academy of Sciences 329:14-29.
610
611 Seeger, R., Lehmann, R., 2011. Driving ability and fitness to drive in people with diabetes mellitus.
612 Therapeutische Umschau 68:249-52.
613
614 Sénéchal, M., Johannsen, N.M., Swift, D.L., Earnest, C.P., Lavie, C.J., Blair, S.N., Church, T.S., 2015.
615 Association between changes in muscle quality with exercise training and changes in cardiorespiratory
616 fitness measures in individuals with type 2 diabetes mellitus: Results from the HART-D study. PloS one
617 10:e0135057.

Shun, C.T., Chang, Y.C., Wu, H.P., Hsieh, S.C., Lin, W.M., Lin, Y.H., Tai, T.Y., Hsieh, S.T., 2004. Skin denervation in type 2 diabetes: correlations with diabetic duration and functional impairments. Brain 127:1593-605.

Siegler, I., Reymond, G., Kemeny, A., Berthoz, A., 2001. Sensorimotor integration in a driving simulator: contributions of motion cueing in elementary driving tasks, Proceedings of Driving Simulation Conference, pp. 21-32.

Simoneau, G.G., Ulbrecht, J.S., Derr, J.A., Cavanagh, P.R., 1995. Role of somatosensory input in the control of human posture. Gait & posture 3:115-22.

Spiess, K.E., Sansosti, L.E., Meyr, A.J., 2017. Diabetic driving studies—part 2: a comparison of brake response time between drivers with diabetes with and without lower extremity sensorimotor neuropathy. The Journal of Foot and Ankle Surgery 56:573-76.

Vaz, M.M., Costa, G.C., Reis, J.G., Junior, W.M., De Paula, F.J.A., Abreu, D.C., 2013. Postural control and functional strength in patients with type 2 diabetes mellitus with and without peripheral neuropathy. Archives of Physical Medicine and Rehabilitation 94:2465-70.

Wilson, M., Stephenson, S., Chattington, M., Marple-Horvat, D., 2007. Eye movements coordinated with steering benefit performance even when vision is denied. Experimental brain research 176:397-412.

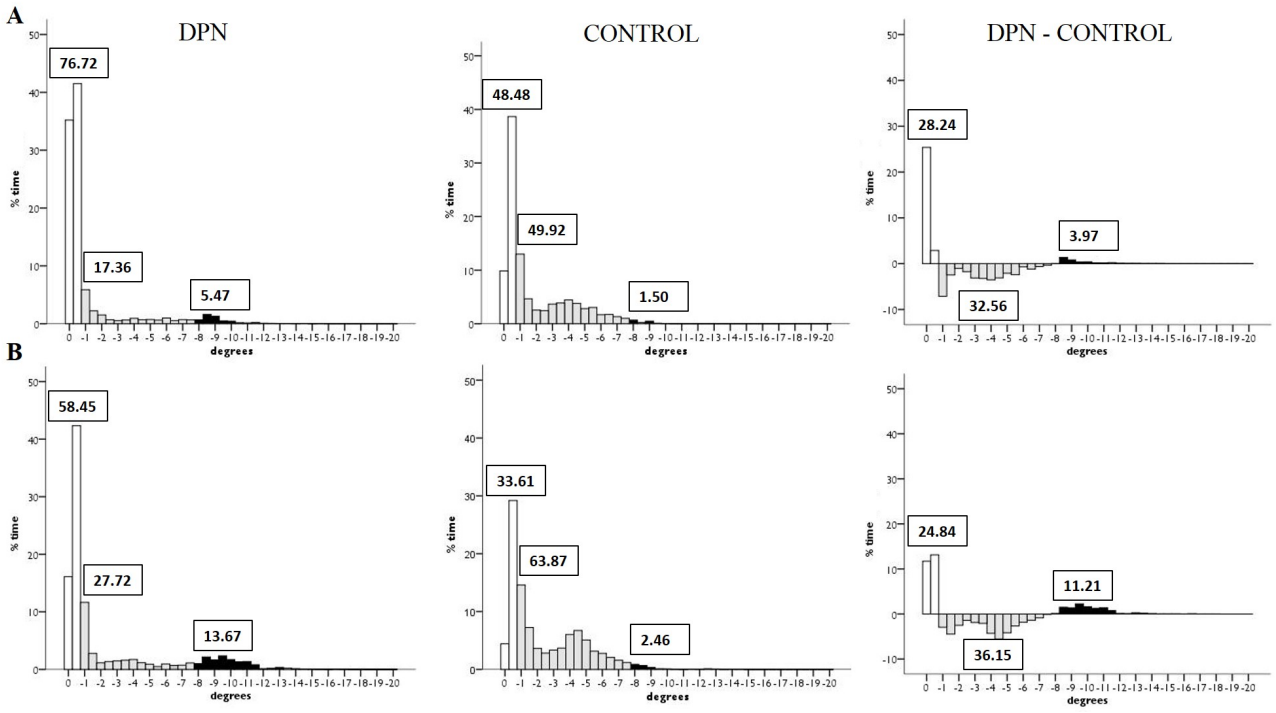

Figure 1: Accelerator pedal position frequency distribution plots during the first drive (Row **A**) and the second drive (Row **B**). Each bar represents the time (seconds) the accelerator pedal spent in a specific position, from 0 (no displacement of the pedal) to a maximum of -20° (maximal depression of the pedal) during driving. The change in the colours highlights the transition between the three pedal regions: high (white bars), mid (grey bars) and low (black bars) ranges. The numbers inside the boxes represent the % of time spent in each specific region of the pedal range. Each panel should be read from left to right. The plots on the left represent the original frequency distribution plot of the patients with diabetic peripheral neuropathy (DPN), the plots in the middle indicate the original frequency distribution plot of control subjects (CONTROL) and the plots on the right show the "difference plot" obtained by subtracting one group plot from another (DPN-CONTROL).

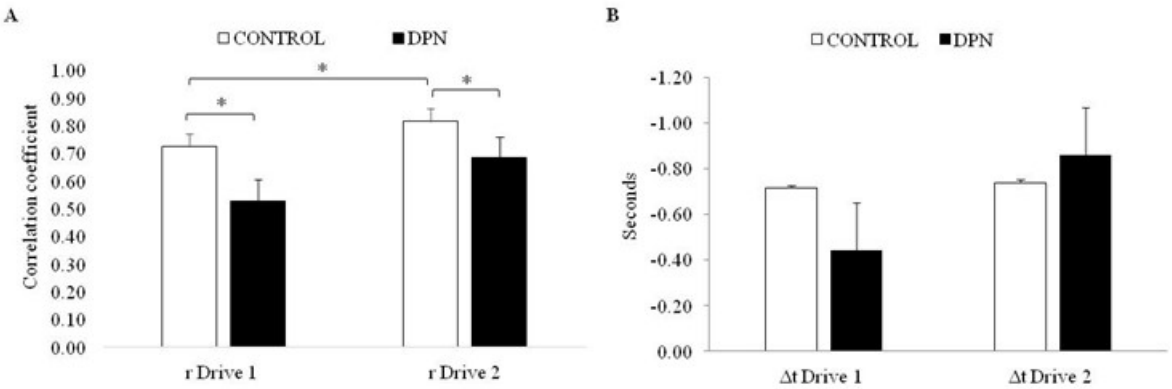

Figure 2: - A. Eye-steering correlation coefficient "r" during the first drive (r Drive 1) and the second drive (r Drive 2) in each group: control subjects in white (Control) and patients with diabetic peripheral neuropathy in black (DPN) **B.** Time lead values (Δt, seconds) during the first (Δt Drive 1) and second (Δt Drive 2) drives in each group: control subjects in white (Control) and patients with diabetic peripheral neuropathy in black (DPN). Values are means and SD. *Significantly different ($p<0.05$).

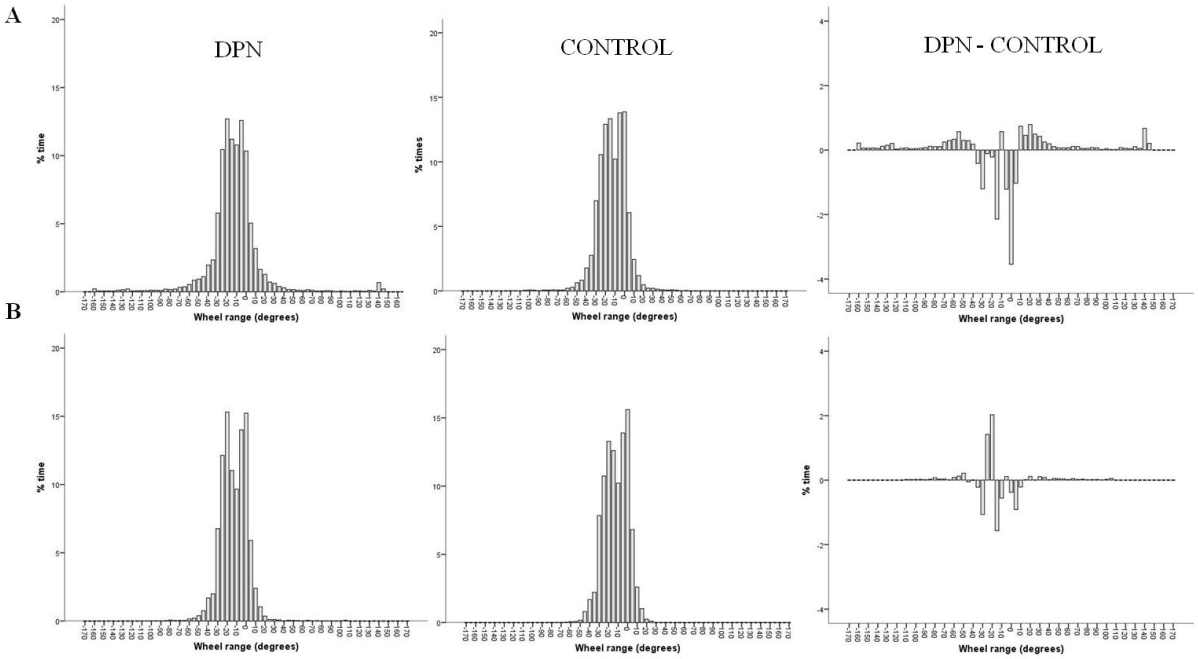

Figure 3: Frequency distribution plots of the steering wheel position during the first three minutes (familiarization) of the first drive (**A**) and of the second drive (**B**). Each bar represents the time (seconds) the steering wheel spent in a specific position. Each panel should be read from left to right. The plots on the left represent the original frequency distribution plot of the patients with diabetic peripheral neuropathy (DPN), the plots on the middle indicate the original frequency distribution plot of control subjects (CONTROL) and the plot on the right show the "difference plot" obtained by subtracting one group plot from another (DPN-CONTROL).

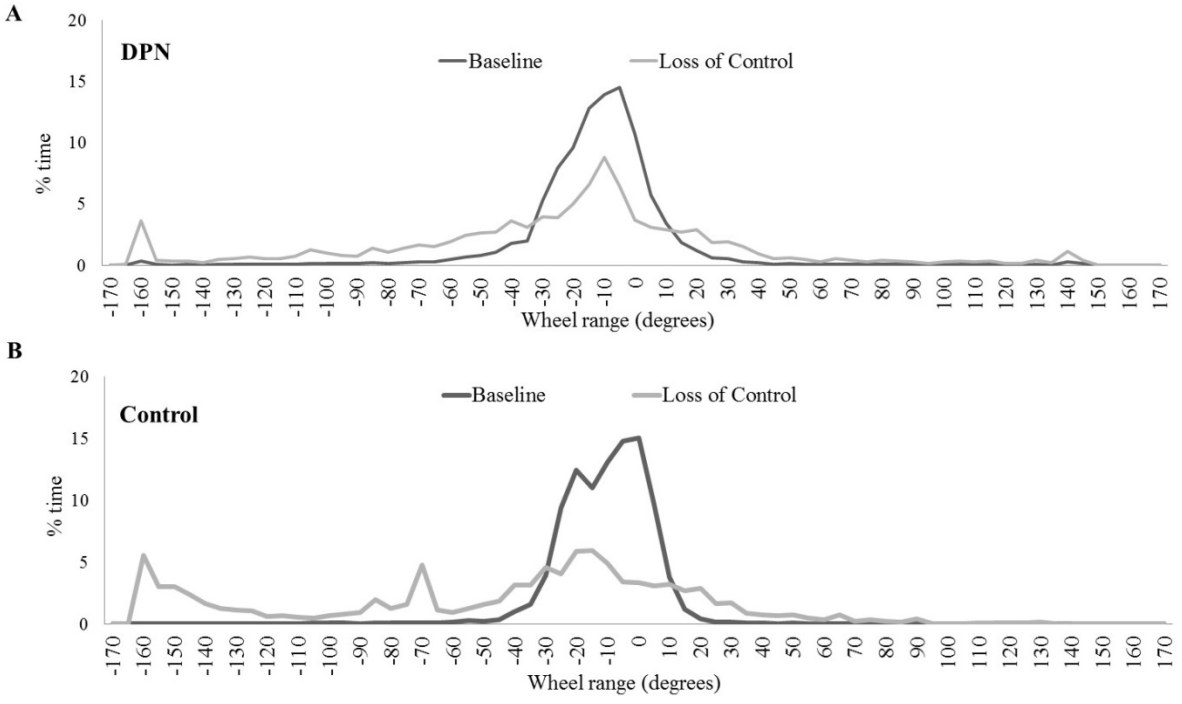

Figure 4: The two graphs represent the % of time the steering wheel was in a specific position during a loss of control event (grey lines) or in a baseline condition (black lines) in patients with diabetic peripheral neuropathy (DPN) (**A**) and in the control subjects (Control) (**B**).